PART ONE
REARRANGEMENT OF β-CHLOROALKYLAMINES; RING EXPANSION BY REARRANGEMENT OF THE β-CHLOROALKYLAMINO GROUP

PART TWO
THE SYNTHESIS OF α-AMINO-β-HYDROXY ACIDS

BY

CHARLES LEON ZIRKLE

B.S., Indiana University, 1942

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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PART ONE

REARRANGEMENT OF β-CHLOROALKYLAMINES; RING EXPANSION BY REARRANGEMENT OF THE β-CHLOROALKYLAMINO GROUP

Introduction

Recently it was found that 2-hydroxyisopropyl sulfides yield, upon treatment with hydrochloric acid or thionyl chloride, not the expected 2-chloroisopropyl sulfides but the isomeric 2-chloro-*n*-propyl sulfides (1). The rearrangement is believed to occur through an intermediate cyclic sulfonium chloride. This investigation was undertaken to determine whether β-chloroalkylamines and β-chloro cyclic imines undergo a similar rearrangement through an ethyleneimonium ion intermediate. Such a transformation in the latter amines would lead to enlargement or contraction of the imine rings.

Discussion Of Results

When the hydrochloride (I) of 2-diethylamino-1-chloropropane (II), prepared from 2-diethylamino-1-propanol hydrochloride by treatment with thionyl chloride, was treated with alkali, the free base obtained was 1-diethylamino-2-chloropropane (III), instead of II. That II did not rearrange when in the form of its salt (I) was demonstrated by the fact that the picrate formed from the salt was different from that obtained from the free amine. 1-Diethylamino-2-chloropropane (III), prepared from 1-diethylamino-2-propanol hydrochloride, did not rearrange when liberated from its hydrochloride (IV). The free amine formed a picrate identical with that of the original amine salt (IV) and that of the free base obtained from 2-diethylamino-1-chloropropane hydrochloride (I). The isomeric hydrochlorides (I and IV) and a mixture of the two have the same melting point, indicating that I is rearranged by heat.

Similarly, when the hydrochloride (V) of 1-ethyl-2-chloromethylpyrrolidine (VI), obtained from the corresponding amino alcohol hydrochloride by the action of thionyl chloride, was treated with alkali, the free base isolated was not VI but 1-ethyl-3-chloropiperidine (VII). VII, prepared by treatment of 1-ethyl-3-hydroxypiperidine hydrochloride with thionyl chloride, did not rearrange when liberated from its salt (VIII). The free amine was identical with that obtained from 1-ethyl-2-chloromethylpyrrolidine hydrochloride (V). The pyrrolidine salt (V) is isomerized to 1-ethyl-3-chloropiperidine hydrochloride (VIII) by heat. These results were demonstrated by the methods described above.

A cyclic ethyleneimonium ion has been proposed as an intermediate in these rearrangements.

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PART TWO

THE SYNTHESIS OF α-AMINO-β-HYDROXY ACIDS

Introduction

Dihydrosphingosine, a base found in the hydrolysates of certain lipids in nerve tissue, has recently been identified as 1,3-dihydroxy-2-amino-octadecane (1). As a method of approaching the synthesis of compounds of this type, the reduction of the corresponding α-amino-β-hydroxy esters offers considerable promise (2). One of the most direct procedures for obtaining the intermediate α-amino-β-hydroxy acids appeared to be the amination of α-bromo-β-hydroxy acids. However, the latter compounds, when treated with ammonia are converted into glycidic acids, which in certain cases add ammonia or amines at the β-carbon to form β-amino-α-hydroxy

acids instead of the desired α-amino compounds (3). This investigation was undertaken to study this reaction further and to find a satisfactory method for preparing α-bromo-β-hydroxy acids.

Discussion Of Results

By passing the theoretical amount of bromine vapor into an aqueous solution of crotonic acid, a high yield of the crude hypobromous acid addition product was obtained, together with a small amount of α,β-dibromobutyric acid. The crude product was easily purified to give α-bromo-β-hydroxy-*n*-butyric acid (4) in 79% yield. Only one racemic form of the bromohydroxy acid, m.p. 86-87°, was isolated from the reaction mixture.

It was found that α-bromo-β-hydroxy-*n*-butyric acid reacts smoothly with aqueous ammonia either at room temperature or at 65-75° giving the aminohydroxy acid in 80-90% yield. Benzoylation of the crude product by the method of Carter and Stevens (5) gave N-benzoyl-DL-allothreonine in 90% yield. The unrecrystallized derivative melted at 173-174° (pure N-benzoyl-DL-allothreonine melts at 176-177°). The recrystallized derivative and its mixture with an authentic sample of N-benzoyl-DL-allothreonine melted at 176-177°. Several attempts were made to isolate other benzoyl derivatives from the mother liquors but with no success. No evidence was obtained for the presence of β-amino-α-hydroxy acids or of DL-threonine.

This method for preparing DL-allothreonine is a considerable improvement over the previous syntheses (6,7) since it involves fewer steps, gives higher yields, and the crude product does not contain appreciable amounts of any of the other aminohydroxybutyric acids.

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VITA

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